IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Ashley Birkett	PATENT
Serial No.:	09/930,915	Attorney Docket LOR-102.2 (9720/81175)
Filed:	August 15, 2001	
For:	IMMUNOGENIC HBc CHIMER PARTICLES HAVING ENHANCED STABILITY	Group Art No. 1648
Examiner:	Bo Peng	

APPELLANT'S BRIEF ON APPEAL

This is an Appeal from the Office Action mailed March 4, 2009, at least twice and finally rejecting claims 1-9, 12-33, 35-38, and 42-78. A Notice of Appeal was filed on September 1, 2009. A Petition for a four month Extension of Time and its required fee are enclosed. Applicable fees accompany the filing of this brief.

Should there be any deficiency in fees in connection with this Appeal, the Commissioner is respectfully requested to and is hereby authorized to charge any such deficiency in fees to Deposit Account No. 23-0920.

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STATEMENT OF THE REAL PARTY IN INTEREST

Celldex Therapeutics, Inc., the assignee, is the real party in interest.

STATEMENT OF RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

JURISDICTIONAL STATEMENT

This appeal is taken under 35 U.S.C. §134(a). This is an appeal from the Office Action mailed March 4, 2009, at least twice and finally rejecting claims 1-9, 12-33, 35-38, and 42-78.

STATUS OF CLAIMS

Claims 1-9, 12-33, 35-38, and 42-78 are pending and have been at least twice and finally rejected. The rejections of claims 1-9, 12-33, 35-38, and 42-78 are being appealed. A copy of the pending claims appears in the Claims Appendix.

STATUS OF AMENDMENTS

There amendments in the last Response of February 2, 2009 by Applicant were entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject application was published as Pub. No. US 20030138769, and citation will be made to the paragraphs of that publication.

The present invention contemplates a recombinant hepadnavirus nucleocapsid protein; i.e., a hepatitis B core (HBc) chimeric protein [or chimer hepatitis B core protein molecule or HBc chimer molecule or just chimer] that self-assembles into particles after expression in a host cell. The chimeric protein (i) displays one or more immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or has a heterologous linker residue for a conjugated epitope in the immunogenic loop, and contains a cysteine residue at or near the

C-terminus that confers enhanced stability to the particles. The chimeric protein is sufficiently free of arginine residues toward the C-terminus so that the self-assembled particles are substantially free of nucleic acid binding. **[par.0019]**

The present invention also contemplates an immunogenic particle comprised of recombinant hepatitis B core (HBc) chimeric protein molecules. The chimeric protein (i) displays one or more immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or (ii) has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop. That recombinant protein contains a cysteine residue at or near the C-terminus. The particles are substantially free of nucleic acid binding and exhibit enhanced stability relative to particles comprised of otherwise identical proteins that are free of the cysteine residue. **[par.0020]**

One embodiment of the invention contemplates a recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that **[par.0021]**

(a) contains (i) a sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule including a covalently linked peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or (ii) a

sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues, **[par.0022]**

(b) contains one to ten, and more preferably, one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence present and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], and **[par.0023]**

(c) contains a sequence of at least five amino acid residues from HBc residue position 135 to the HBc C-terminus. **[par.0024]**

The contemplated chimer molecules (i) contain no more than 20 percent substituted amino acid residues in the HBc sequence, and (ii) self-assemble on expression in a host cell into particles that are substantially free of binding to nucleic acids. Those particles are also more stable than are particles formed from an otherwise identical HBc chimer that lacks the above C-terminal cysteine residue(s) or where a C-terminal cysteine residue is present in the chimer and is replaced in an otherwise identical chimer molecule by another residue such as an alanine residue. **[par.0025]**

In one aspect of this embodiment, a contemplated HBc chimer has a sequence of about 135 to about 515 amino acid residues and contains four serially peptide-linked domains that

are denominated Domains I, II, III and IV. From the N-terminus, Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of about position 5 through position 75 of HBc, and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4. Domain II comprises 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all, and preferably at least 4, residues in a sequence of HBc positions 76 to 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous (foreign) to HBc and constitute a heterologous epitope such as a B cell epitope or a heterologous linker residue for an epitope such as a B cell epitope or (ii) the sequence of HBc at positions 76 to 85 is present free from heterologous residues. Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II. Domain IV comprises (i) zero through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten, and more preferably one to three, cysteine residues peptide-bonded C-terminal to that HBc sequence [C-terminal cysteine residue(s)] and (iii) zero to about 100, more preferably zero to about 50, and most

preferably about 25 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including the above one to ten cysteine residues of (ii). **[par.0026]**

A contemplated recombinant chimer protein forms particles that are substantially free of binding to nucleic acids and are more stable than are particles formed from a HBc chimer containing the same peptide-linked Domain I, II and III sequences and a Domain IV sequence that is otherwise same but lacks any cysteine residues or in which a cysteine residue is replaced by another residue such as an alanine residue. When chimer molecules are assembled into particles, those particles exhibit an absorbance ratio at 280 nm to 260 nm (280/260 absorbance ratio) of about 1.2 to about 1.7. The particles formed are believed to be of the T = 4 structure, containing 240 monomeric HBc chimers or 120 dimer HBc chimers. **[par.0027]**

More broadly, a contemplated chimer particle comprises a C-terminal truncated HBc protein (to at least residue 149) that contains a heterologous epitope or a heterologous linker residue for an epitope in the immunodominant loop, or an uninterrupted immunodominant loop, and regardless of the amino acid residue sequence of the immunodominant loop, one to three

C-terminal cysteine residues heterologous to the HBc sequence. Such a particle exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7 and is more stable than a particle formed from an otherwise identical HBc chimer that lacks the above C-terminal cysteine residue(s) or where a single C-terminal cysteine residue is present in the chimer and is replaced by another residue. **[par.0028]**

Another embodiment comprises an inoculum or vaccine that comprises an above HBc chimer particle or a conjugate of a hapten with an above HBc chimer particle that is dissolved or dispersed in a pharmaceutically acceptable diluent composition that typically also contains water. When administered in an immunogenic effective amount to an animal such as a mammal or bird, an inoculum (i) induces antibodies that immunoreact specifically with the chimer particle or the conjugated (pendently-linked) hapten or (ii) activates T cells, or (iii) both. The antibodies so induced also preferably immunoreact specifically with (bind to) an antigen containing the hapten, such as a protein where the hapten is a peptide or a saccharide where the hapten is an oligosaccharide. **[par.0029]**

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

2) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

3) Whether Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561).

4) Whether Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) as applied to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Thorton et al (US 5,143,726).

5) Whether Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are unpatentable under 35 U.S.C. §103 as being obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) as applied

to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Birkett et al (US 6,231,864).

6) Whether Claims 1-9, 12-33, 35-38 and 42-78 are unpatentable under obviousness-type double patenting, as being obvious over (1) claims 1-46 of co-pending application 10/732,862; (2) claims 1-53 of 10/787,734; (3) claims 98-109 of 10/805,913; (4) claims 79-115 of 10/806,006; (5) claims 47-85 of 11/508,655; (6) claims 1-22, 25, 26 of 11/507,083.

7) Whether Claims 1-9, 12-33, 35-38, and 42-78 are unpatentable under obviousness-type double patenting, as being obvious over (1) claims 1-19 of U.S. Patent No. 6,213,864 in view of Zlotnick et al. (PNAS, 1997, 94 (18): 9556-61).

STATEMENT OF FACTS

The captioned application was filed on August 15, 2001 and is a continuation-in-part of Application No. 60/266,867, filed on August 22, 2000, which claimed priority to Application No. 60/225,843, filed on August 16, 2000. The captioned application was published as Pub. No. US20030138769, and citations will be made to the paragraphs of that publication.

ARGUMENT

1) Claims 1-9, 12-33, 35-38, and 42-78

Comply with the Enablement Requirement

In contrast to allegations asserted in the Final Office Action, Claims 1-9, 12-33, 35-38, and 42-78 do satisfy the enablement requirement. The facts are that the Office Action of March 4, 2009 rejected Claims 1-9, 12-33, 35-38, and 42-78 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement for reasons set forth in Office Action dated August 4, 2008, par. 5-9. (See page 2, sections 5-8 of Office Action of 3-4-09.)

In that Action, it was alleged that the specification, while being enabling for a HBc chimer of SEQ ID NO:246-251, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NO:246-251 and having enhanced stability. It was also alleged that the specification does not enable any person skilled in the art to make the invention commensurate in scope with the claims. This rejection cannot be agreed with.

The current claims have a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop*. This limitation has not been taken into account in the Action's arguments. The current claims also have a limitation of *containing 1-10 cysteine*

residues at the C-terminus. This limitation also has not been taken into account by the Action.

Therefore, at the outset, the Action's arguments do not pertain to the current set of claims.

The Action also alleged that the Applicant has not disclosed sufficient species of alternative HBc variants that have 5% substitution and enhanced particle stability.

Please see Figures 3 and 8 and relative Examples, which provide evidence of chimeric particles having enhanced stabilities. Fig. 3 is a photograph of an SDS-PAGE analysis under reducing conditions to show the stabilizing effects on expressed particles of a codon for a single cysteine residue inserted in frame between the C-terminal codon (V149) and the termination codon of HBc in a chimer that also contains $(NANP)_4$ inserted between the amino acids of positions 78 and 79 (V2.Pf1+C), and a similar construct whose C-terminus is residue V149 (V2.Pf1) at day zero and after 15 days at 37°C. [Lane 1, V2.Pf1 - day 0; Lane 2, V2.Pf1 - day 15 at 37°C; Lane 3, V2.Pf1+C, day 0; Lane 4, V2.Pf1+C - day 15 at 37°C.]

As can readily be seen in Figure 3, the two particles (with and without cysteine) started out similarly. However, after 14 days at 37°C, the cysteine-containing particle (V2.Pf1+C) exhibited fewer bands on the SDS gel than the

particle without (V2.Pf1), indicating enhanced stability as compared to the particle lacking the added cysteine residue. (see Example 6 and [par. 0358])

Figure 8 is a photograph of an SDS-PAGE analysis under reducing conditions following incubations at 37°C for 0, 1 and 2 days that illustrates the stabilizing effects on (1) chimer HBc149 particles containing the *P. falciparum* $(NANP)_4$ immunogenic sequence inserted between HBc amino acid residues 78 and 79 that also contain a carboxy-terminal universal *P. falciparum* malarial T cell epitope peptide-bonded to HBc position 149 [UTC; V12.Pf1 = V2.Pf1 + Pf/CS-UTC], and (2) similar particles in which the cysteine at position 17 of the UTC was mutated to be an alanine residue and a cysteine residue was added at residue position 150, between the HBc residue at position 149 and the beginning of the UTC [V12.Pf1(C17A)+C150].

Results of densiometric analysis of that SDS-PAGE gel are shown in Table 19. The particles having a C-terminal cysteine, V12.Pf1 and V12.Pf1(C17A)+C150, were still full length at 93% and 63% respectively, whereas the non-cysteine containing particles were only 1% full length.

The data from this study are interpreted to mean that the C-terminal cysteine-stabilized particles are more stable immediately on production as well as after incubation at 37°C for

various time periods. The stabilized particles also exhibit enhanced immunogenicity even in the absence of adjuvant. (see Example 22 and 23)

In addition to this evidence, the "Definitions" section of the present application, under the term "corresponds" states that peptide sequences described contain only conservative substitutions along the polypeptide sequence. (See par. [0055].) Furthermore, in par. [0152], the specification relates that the contemplated chimers contain conservative substitutions in the amino acid residues that constitute domains I-IV of the HBc sequence. Also, paragraph [0153] states that guidance in determining which amino acid residues can be substituted, inserted or deleted without abolishing biological activity or particles formation can be found using computer programs known in the art such as LASERGENE. Still further, paragraph [0156] states that substitutions are preferably in the non-helical portions of the molecule between residues 2-15 and 24-50 to help assure particle formation, citing Koschel et al., (1999) *J. Virol.*, 73(3): 2153-2160.

Simply put, the above passages illustrate that the specification describes and enables chimeric HBc molecules with conservative amino acid substitutions that retain biological activity and structural integrity. Based upon these passages,

it is submitted that one of ordinary skill in the art would be able to make and use such HBc chimers.

In specific detail, the specification points out that the amino acid substitutions are to be up to 5% of the sequence, that the substitutions are to be conservative, that guidance as to proper conservative substitutions can be obtained with LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation.

A contemplated chimer of 149 HBc residues can therefore contain up to about 30 residues that are different from those of SEQ ID NO:247 at positions 1 through 149, and preferably about 15 residues. More preferably, about 7 or 8 residues are different from the *ayw* sequence (SEQ ID NO:247) at residue positions 1-149, and most preferably about 4 or 5 residues are different. [par. 0156]

It is submitted that these examples of illustrative substitutions are more than a sufficient number to constitute enablement.

The CCPA long ago held that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim. *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).

Therefore, it is respectfully requested that this rejection be withdrawn.

2) Claims 1-9, 12-33, 35-38, and 42-78 Comply with the Written Description Requirement

In contrast to allegations asserted in the Final Office Action, Claims 1-9, 12-33, 35-38, and 42-78 do satisfy the written description requirement. The facts are that the Office Action of March 4, 2009 rejected claims 1-9, 12-33, 35-38, and 42-78 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Action alleged that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

The arguments and evidence presented in the Action do not make sense with regard to the current application. In section 10 on page 5 of the Action, it is argued that:

> [i]n support of the claims, the specification shows a few species of HBc chimer (for example, 7 of 24 chimers in Example 14) were able to yield particles, see Table 13, Example 14. Of the modified HBc chimers in the above example, however, 14 of the 24 tested lost their ability to form particles. Thus, the specification shows that it is uncertain if HBc chimers containing a 5% substitution frequency in

> SEQ ID NO:246-251 can form viral-like particles as can HBc, or would the resultant HBc particles have enhanced stability as claimed.

This argument is completely off-base. Example 14 does not discuss 24 chimers nor does Table 13 show results for them. There is no evidentiary basis for the Action's allegations. As such, it is respectfully requested that this rejection be withdrawn. It is rather submitted that this basis for rejection was inadvertently taken from another Action.

As to the allegations in section 11, that a single amino acid change can result in the loss of peptide function, this is not on point either. The claims are not directed to randomly substituted amino acid sequences. The specification points out that the amino acid substitutions are to be up to 5% of the sequence, that the substitutions are to be conservative, that guidance as to proper conservative substitutions can be obtained with LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation.

The current claims also have a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop*. This limitation has

not been taken into account in the Action's arguments. The current claims also have a limitation of *containing 1-10 cysteine residues at the C-terminus*. This limitation also has not been taken into account by the Action.

As described in the previous section of this Brief, ample data has been provided to show that the Applicant was indeed in possession of the claimed invention. (See Figures 3, 7, and 8). Therefore, it is respectfully requested that this rejection be withdrawn.

3) A Prima Facie Case of Obviousness of Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 Has Not Been Established

In contrast to allegations asserted in the Final Office Action, Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 are not obvious over the teachings of Pumpens in view of Zlotnick. The facts are that the Office Action of March 4, 2009 rejected claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 under 35 U.S.C. §103, as obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561). The Action alleged that this rejection is maintained for the reasons

of record. (See page 7, sections 15-17 of Office Action of 3-4-09.)

Pumpens does not teach adding 1-10 C-terminal cysteines to stabilize the chimeric molecule.

Zlotnick does not teach a conjugated epitope present in the HBc immunodominant loop in conjunction with 1-10 cysteine residues at the C-terminus of the particle and that these particles are more stable than chimers without the C-terminal cysteine residues.

It must be noted that the reliance on Fig. 1 of Zlotnick is misplaced. Zlotnick teaches substitution of Cys48, Cys61, Cys107, and Arg150. The present invention does not require these substitutions. There is no suggestion in Zlotnick to make the present chimers as recited in the claims.

There is also a significant problem with Fig. 1 of Zlotnick upon which the Action heavily relies in its arguments. There is no control molecule such as Cp150 in the set of molecules made. For instance, in the Cp149 series of molecules, there is the Cp149 molecule with no amino acid substitutions. There also is the Cp*149 molecule that has 3 cysteine substitutions. Therefore, one of ordinary skill could compare the effects of the cysteine substitutions with the properties of the unsubstituted molecule, Cp149. However, in the case of

Cp*150, there are 4 amino acid substitutions and no control molecule of 150 amino acids with no amino acid substitutions with which to compare. Therefore it is impossible to accurately state what the effects of those 4 amino acid substitutions are on the molecule.

An acknowledgement of the importance of molecule length is made by Zlotnick when he states that truncating the protein by two residues renders it incapable of assembly (see page 9556, second col., first paragraph). Therefore, it is necessary to have a control molecule of the same amino acid length, such as Cp150, in order to glean any accurate information about the effects of those 4 amino acid substitutions in the Cp*150 molecule. One of skill in the art would also recognize that in order to make any conclusions about the effect of a C-terminal cysteine, there would have had to be a second Cp150 control, where all the cysteines remain unchanged and only the Cp150 C-terminal amino acid is changed. With this molecule to compare with, one of skill in the art could accurately determine the changes in stability due to the presence or absence of a C-terminal cysteine. As it stands, there is no comparison to be made, so no reliable conclusions can be drawn.

In this regard and in response to previous arguments made in previous Responses, the Action maintained that this was a peer-review, published journal so the results are not suspect. This belief is completely off-base and irrelevant. One of skill in the art would not believe anything and everything simply because it has been produced in a peer-reviewed journal. It is common knowledge that one of skill in the art routinely disbelieves and disagrees with evidence presented in a published journal. Still further, some of the most eminent peer-reviewed journals have recently published retractions of previously well heralded articles, such as the stem cell paper from Hwang Woo-suk and co-workers that was retracted from *Science* in 2006.

Next, the Action incorrectly argues that Zlotnick teaches that the addition of a heterologous cysteine residue at the C-terminus results in dimer formation and enhanced stability (citing page 9558, par. 1 and 2). This allegation is not true. First, Zlotnick states that purified Cp*149 and Cp*150 assemble into capsids *under the same conditions* as other Cp constructs. (See page 9558, first par.) Surely one of skill in the art would recognize that if there were some stability enhancement due to the presence of the C-terminal Cys, there would also most likely be some difference in the conditions of particle assembly. There is none and that speaks to teaching no

advantage as to having a C-terminal chimer. Moreover, Zlotnick emphasizes that these capsids were *indistinguishable* by negative staining electron microscopy and sedimentation on sucrose gradients. Again this teaches one of skill in the art that there seems to be no advantage in having a C-terminal cysteine.

In fact, it is equally plausible that the substitution of arginine with another amino acid at the C-terminus led to increased stability of that molecule. It is conceivable that the C-terminal arginine is destabilizing to the molecule. This is especially plausible in the absence of a proper control molecule, as stated above. Cp149 is not a proper control for Cp*150. The length is not the same. As such, it cannot be reasonably concluded by one of skill in the art that the C-terminal cysteine was responsible for the alleged increased stabilization. It must be noted that Zlotnick was not looking for ways to increase the stability of capsid particles, and that is probably why he chose not to issue such a conclusion, especially in the absence of proper controls.

Truly, Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly. He states that binding of Au11 (monomaleimidyl-undecagold) to Cp*150 induces capsid assembly. He suggests that this binding of Au11 may induce small changes in molecular surfaces near the C-

terminus that dock together when dimmers polymerize and stimulate the assembly process. (See page 9560, col. 2, first par.) Zlotnick states that the data show that the gold cannot cross-link subunits nor coordinate C-terminal cysteines, yet the binding of Au11 to Cp*150 induces capsid assembly. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that they are not so important.

All in all, Zlotnick does not provide valid support for the premise that C-terminal cysteines enhance stability because Zlotnick's data lacks the proper controls. As a consequence, conclusions gleaned from it are suspect. Furthermore, Zlotnick himself suggests that other factors come into play regarding inducing capsid assembly and stability, such as changes in molecular surfaces.

Moreover, Zlotnick makes no mention of the insertion of foreign epitopes at the internal loop of the HBc sequence as is recited in the present claims.

Therefore, the present claims are not prima facie obvious over Pumpens in view of Zlotnick. Putting all of these teachings together, a skilled worker would not know what to keep in and what to take out without looking at the present

specification. Such hindsight reconstruction is inappropriate. It is respectfully requested that this rejection be withdrawn.

4) A Prima Facie Case of Obviousness of Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 Has Not Been Established

Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are not obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) as applied to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Thorton et al. (US 5,143,726) as alleged in the Action. The facts are that the Office Action of March 4, 2009 rejected claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 under 35 U.S.C. §103, as obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) further in view of Thorton et al (US 5,143,726). The Action alleged that this rejection is maintained for the reasons of record. (See page 7, sections 18-20 of Office Action of 3-4-09.)

The teachings and shortcomings of Pumpens and Zlotnick when combined have previously been presented above. In short, Pumpens does not teach adding 1-10 C-terminal cysteines to stabilize the chimeric molecule. Further, Zlotnick does not teach a conjugated epitope present in the HBc immunodominant

loop in conjunction with 1-10 cysteine residues at the C-terminus of the particle and that these particles are more stable than chimers without the C-terminal cysteine residues. Putting the two teachings together does not lead to the claimed invention without hindsight.

Thorton, likewise, does not teach the placement of C-terminal cysteines that stabilize a polypeptide molecule. The Action argued that Thorton specifically teaches a polypeptide immunogen operatively linked by a peptide bond to an N-terminal flanking sequence, or C-terminal flanking sequence of HBc, or HBV core protein from about position 70 to about position 140 from the amino terminus thereof. This is a vague argument. Specifically, in column 9, lines 59-63, Thorton states:

> [t]hus, the present invention contemplates an immunogenic polypeptide conjugate comprising a HBcAg protein operatively linked though an amino acid residue side chain to a polypeptide immunogen.

In contrast, the present invention does not utilize an endogenous amino acid side chain for linking. The present invention utilizes a heterologous linker residue (see claim 12). Therefore, that which Thorton is teaching is different from that which is being used in the present invention.

Also, the Action argues that the chemically modified residues are functional equivalents of a heterologous linker

residue, citing the last paragraph in col. 14 bridging to col. 15 as support. This alleged equivalency is disagreed with. First of all, no heterobifunctional agents which generate disulfide links, such as the chemical, N-succidimidyl-3-(2-pyridyldithio)-proprionate are used for any purpose in the present invention. This reagent creates disulfide linkages between itself and a cysteine residue in one protein and an amide linkage through the amino on a lysine or other free amino group in the other. It is unknown how these reagents would interact with the present chimeric particles sequences that contain multiple cysteine groups, unlike those of Thorton. Nor are any thioether-forming reagents used in the present invention. These are also bifunctional coupling reagents and it is unclear as to how such a chemical would interact with the present chimeric particles that contain multiple cysteine groups, unlike those of Thorton.

It is not agreed with that the chemical modification of a peptide would produce a reasonable expectation of success in the mind of a worker of ordinary skill in the art. The chemical entities and how they may function with the claimed molecules are questionable at best. Thorton does not teach or suggest that these are equivalent. Thus, the rejection based on Pumpens in view of Zlotnick and Thorton should be withdrawn.

5) A Prima Facie Case of Obviousness of Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 Has Not Been Established

Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are not obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) as applied to claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58 63-75, 77 and 78, further in view of Birkett et al. as alleged in the Action. The facts are that the Office Action of March 4, 2009 rejected claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 under 35 U.S.C. §103, as obvious over Pumpens et al. (*Intervirology*, 1995, vol. 33, pp63-74) in view of Zlotnick et al. (*PNAS*, 1997, vol. 94, pp9556-9561) further in view of Birkett et al (US 6,231,864).

The Action alleged that the Birkett patent above has a common inventor with the instant application. Based upon the earlier effective filing date of the Birkett patent, it constitutes prior art only under 102(e), according to the Action.

It is submitted that there is no basis to believe that inasmuch as only one person, Ashley J. Birkett, is a named inventor of both the patent and this application that they are different persons named Ashley J. Birkett who are doing the same

type of work. No showing is believed necessary under 37 C.F.R. 1.132.

Therefore, because the prior art is not "by another" as required under 35 U.S.C. 102(e), there is no basis for this rejection. It is respectfully requested that this objection be removed.

6) Claims 1-9, 12-33, 35-38 and 42-78 Are Not Obvious under the Doctrine of Obviousness-Type Double Patenting

The Action asserted that claims 1-9, 12-33, 35-38 and 42-78 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-78 of 09/930,915; (2) claims 1-53 of 10/787,734; (3) claims 98-109 of 10/805,913; (4) claims 79-115 of 10/806,006; (5) claims 47-85 of 11/508,655; (6) claims 1-22, 25, 26 of 11/507,083.

The Examiner's comments about obviousness-type double patenting are noted. It must be pointed out that patent application No. 10/805,913 has been abandoned; patent application No. 10/806,006 has been abandoned; and application No. 10/787,734 has issued as U.S. Patent Number 7,361,352. In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the allowed claims and those of the patent. It is believed to

be premature to deal with a terminal disclaimer at the present time.

7) Claims 1-9, 12-33, 35-38 and 42-78 Are Not Obvious under the Doctrine of Obviousness-Type Double Patenting

The Action asserted that claims 1-9, 12-33, 35-38 and 42-78 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-19 of U.S. Patent No. 6,231,864 in view of Zlotnick et al. (PNAS, 1997, 94 (18): 9556-9561).

The Examiner's comments about obviousness-type double patenting are noted. In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time.

CLAIMS SUPPORT SECTION

Claims 1, 18, 42, 51, and 63 are the only independent claims. The rest of the claims are dependent on these claims. Support for each claim in the specification is detailed below.

1. A recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that **[par. 0021]**

(a) contains an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, **[par. 0022]**

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], **[par. 0023]**

(c) contains a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus, **[par. 0024]**

said chimer molecules (i) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles are more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-

terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days. **[par. 0155][par. 0358][par. 0360][par. 0025]**

2. The recombinant HBc chimer protein molecule according to claim 1 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope. **[par. 0028]**

3. The recombinant HBc chimer protein molecule according to claim 2 wherein said heterologous epitope is a B cell epitope. **[par. 0026]**

4. The recombinant HBc chimer protein molecule according to claim 3 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc. **[par. 0083]**

5. The recombinant HBc chimer protein molecule according to claim 3 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present. **[par. 0100]**

6. The recombinant HBc chimer protein molecule according to claim 5 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope. **[par. 0084]**

7. The recombinant HBc chimer protein molecule according to claim 2 further including a peptide-bonded heterologous T cell epitope. **[par. 0083]**

8. The recombinant HBc chimer protein molecule according to claim 7 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue. **[par. 0147]**

9. The recombinant HBc chimer protein molecule according to claim 8 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule. **[par. 0109]**

10-11. (cancelled)

12. The recombinant HBc chimer protein molecule according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope. **[par. 0070]**

13. The recombinant HBc chimer protein molecule according to claim 12 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present. **[par. 0026] [par. 0077]**

14. The recombinant HBc chimer protein molecule according to claim 13 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope. **[par. 0077]**

15. The recombinant HBc chimer protein molecule according to claim 14 that contains the HBc amino acid residue sequence of position 1 through at least position 140, plus a single cysteine residue at the C-terminus. **[par. 0078]**

16. The recombinant HBc chimer protein molecule according to claim 15 wherein said chimer contains the HBc amino acid residue sequence of position 1 through position 149. **[par. 0080]**

17. The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue. **[par. 0104]**

18. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 135 to about 515 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein **[par. 0026]**

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and

optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4; **[par. 0026]**

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) one or more of residues 76 to 85 is absent; **[par. 0026]**

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and **[par. 0026]**

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), **[par. 0026]**

said chimer molecules self-assembling into particles on expression in a host cell, said particles being substantially free of binding to nucleic acids and more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is

assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149. **[par. 0026] [par. 0155] [par. 0358] [par. 0360]**

19. The recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes. **[par. 0083]**

20. The recombinant HBc chimer protein molecule according to claim 19 wherein said two heterologous epitopes are present in Domains I and II, II and IV or I and IV. **[par. 0083]**

21. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope. **[par. 0083]**

22. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a T cell epitope. **[par. 0083]**

23. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous

epitopes is a B cell epitope and the other is a T cell epitope. **[par. 0083]**

24. The recombinant HBc chimer protein molecule according to claim 18 wherein said Domain I includes a heterologous epitope peptide-bonded to one of HBc residues 1-4. **[par. 0026]**

25. The recombinant HBc chimer protein molecule according to claim 24 wherein said heterologous epitope of Domain II is a B cell epitope. **[par. 0084]**

26. The recombinant HBc chimer protein molecule according to claim 25 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149. **[par. 0084]**

27. The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope. **[par. 0028]**

28. The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope comprises up to about 245 amino acid residues. **[par. 0026]**

29. The recombinant HBc chimer protein molecule according to claim 28 wherein said heterologous epitope is a B cell epitope. **[par. 0026]**

30. The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 6 to about 50 amino acid residues. **[par. 0082] [par. 0099]**

31. The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 20 to about 30 amino acid residues. **[par. 0099]**

32. The recombinant HBc chimer protein molecule according to claim 27 wherein said Domain IV comprises 1 to about 5 cysteine residues within about 30 residues from the C-terminus of the chimer molecule. **[par. 0023]**

33. The recombinant HBc chimer protein molecule according to claim 27 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope. **[par. 0084] [par. 0104]**

34. (cancelled)

35. The recombinant HBc chimer protein molecule according to claim 18 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149. **[par. 0080]**

36. The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous linker residue for a conjugated epitope. **[par. 0028]**

37. The recombinant HBc chimer protein molecule according to claim 36 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue. **[par. 0104] [par. 0169]**

38. The recombinant HBc chimer protein molecule according to claim 37 that contains a single cysteine residue at the C-terminus of the HBc chimer protein molecule. **[par. 0094]**

39-41. (cancelled)

42. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 175 to about 240 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein **[pars. 0087, 0108]**

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc; **[par. 0075]**

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope; **[par. 0026]**

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and **[par. 0026]**

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) a cysteine residue [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, **[par. 0026] [par. 0080] [par. 0023]**

said chimer molecules self-assembling into particles on expression in a host cell that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.2 to about 1.6 and are more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149. **[par. 0360][Par. 0358] [Par. 0092] [Par. 00156] [Par. 00155] [par. 0026]**

43. The recombinant HBc chimer protein molecule according to claim 42 wherein said heterologous epitope of Domain II is a B cell epitope. **[par. 0026]**

44. The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 15 to about 50 amino acid residues. **[par. 0099]**

45. The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 20 to about 30 amino acid residues. **[par. 0099]**

46. The recombinant HBc chimer protein molecule according to claim 43 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope. **[par. 0084]**

47. The recombinant HBc chimer protein molecule according to claim 43 wherein said B cell epitope is an amino acid sequence present in a pathogen selected from the group consisting of *Streptococcus pneumonia, Cryptosporidium parvum,* HIV, foot-and-mouth disease virus, influenza virus, *Yersinia pestis, Haemophilus influenzae, Moraxella catarrhalis, Porphyromonas gingivalis, Trypanosoma cruzi, Plasmodium falciparum, Plasmodium vivax, Plasmodium berghi, Plasmodium yoelli, Streptococcus sobrinus, Shigella flexneri,* RSV, *Plasmodium Entamoeba histolytica, Schistosoma japonicum, Schistosoma mansoni,* and ebola virus.**[par. 0102]**

48. The recombinant HBc chimer protein molecule according to claim 43 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.**[par. 0084]**

49. The recombinant HBc chimer protein molecule according to claim 48 wherein said T cell epitope is from the organism against which a contemplated chimer is to be used as an immunogen. **[par. 0110]**

50. The recombinant HBc chimer protein molecule according to claim 43 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule. **[par. 0109]**

51. Immunogenic particles comprising recombinant hepatitis B core (HBc) chimeric protein molecules, said chimeric protein molecules being up to about 515 amino acid residues in length, said chimeric protein molecules **[par. 0021]**

(a) containing an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule, **[par. 0022]**

(b) (i) displaying one or more heterologous immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or (ii) having a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop, **[par. 0023]**

(c) containing a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus, and containing a cysteine residue at or near the C-terminus, **[par. 0024]**

(d) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149, **[pars. 0026, 0155]**

said particle being substantially free of nucleic acid binding and exhibiting enhanced stability relative to particles

comprised of otherwise identical proteins that are free of said cysteine residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days. **[par. 0025] [par. 0358] [par. 0360]**

52. The immunogenic particles according to claim 51 that exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7. **[par. 0027] [par. 0028]**

53. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the N-terminus. **[par. 0019] [par. 0020]**

54. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the C-terminus. **[par. 0019]**

55. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope in the immunogenic loop. **[par. 0019]**

56. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a B cell immunogenic epitope. **[par. 0066]**

57. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a T cell immunogenic epitope. **[par. 0066]**

58. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays separate B cell and T cell immunogenic epitopes. **[par. 0041]**

59. The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop. **[par. 0020]**

60. The immunogenic particles according to claim 59 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue. **[par. 0104]**

61. The immunogenic particles according to claim 60 wherein said heterologous linker residue for a conjugated epitope is conjugated to a hapten. **[par. 0242]**

62. The immunogenic particles according to claim 61 wherein said hapten is an oligosaccharide. **[par. 0242]**

63. Immunogenic particles comprising a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules; **[par. 0020]**

said recombinant chimeric HBc protein molecules having a length of up to about 515 amino acid residues that **[par. 0021]**

(a) contain a HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues, **[par. 0022]**

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], **[par. 0023]**

(c) contain a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus, **[par. 0024]**

said chimer molecules containing no more than 10 percent conservatively substituted amino acid residues in the HBc sequence, and **[par. 0025]**

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from ~~an~~ otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and

incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149. **[par. 0155][par. 0156][par. 0358][par. 0360][par. 0026]**

64. The immunogenic particles according to claim 63 that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6. **[par. 0092]**

65. The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is about 175 to about 240 amino acid residues. **[par. 0087]**

66. The immunogenic particles according to claim 63 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope. **[par. 0028]**

67. The immunogenic particles according to claim 66 wherein said heterologous epitope is a B cell epitope. **[par. 0026]**

68. The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is up to about 435 amino acid residues. **[par. 0108]**

69. The immunogenic particles according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc. **[par. 0026]**

70. The immunogenic particles according to claim 67 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present. **[par. 0104]**

71. The immunogenic particles according to claim 70 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope. **[par. 0099] [par. 0104]**

72. The immunogenic particles according to claim 68 further including a peptide-bonded heterologous T cell epitope. **[par. 0110]**

73. The immunogenic particles according to claim 72 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue. **[par. 0147]**

74. The immunogenic particles according to claim 73 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule. **[par. 0109]**

75. The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 135 to about 515 amino acid residues and

contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein **[par. 0026][par. 0074]**

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4; **[par. 0026]**

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all of the residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBc at positions 76 to 85 is present free from heterologous residues; **[par. 0026]**

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and **[par. 0026]**

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), said chimeric HBc protein having an

amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149. **[par. 0026] [par. 0155]**

76. The immunogenic particles according to claim 75 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.**[par. 0242]**

77. The immunogenic particles according to claim 76 wherein said hapten is a B cell immunogen. **[par. 0242]**

78. The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein **[par. 0087]**

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc; **[par.0075]**

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope; **[par.0026]**

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and **[par.0026]**

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to about five cysteine residues [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, **[par.0026]**

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6, and said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149. **[par. 0092] [par. 0155]**

79-115. (cancelled)

CLAIMS APPENDIX

1. (rejected) A recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that

(a) contains an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop,

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contains a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus,

said chimer molecules (i) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles are more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified

particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days.

2. (rejected) The recombinant HBc chimer protein molecule according to claim 1 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

3. (rejected) The recombinant HBc chimer protein molecule according to claim 2 wherein said heterologous epitope is a B cell epitope.

4. (rejected) The recombinant HBc chimer protein molecule according to claim 3 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

5. (rejected) The recombinant HBc chimer protein molecule according to claim 3 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

6. (rejected) The recombinant HBc chimer protein molecule according to claim 5 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

7. (rejected) The recombinant HBc chimer protein molecule according to claim 2 further including a peptide-bonded heterologous T cell epitope.

8. (rejected) The recombinant HBc chimer protein molecule according to claim 7 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

9. (rejected) The recombinant HBc chimer protein molecule according to claim 8 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

10-11. (cancelled)

12. (rejected) The recombinant HBc chimer protein molecule according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope.

13. (rejected) The recombinant HBc chimer protein molecule according to claim 12 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present.

14. (rejected) The recombinant HBc chimer protein molecule according to claim 13 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope.

15. (rejected) The recombinant HBc chimer protein molecule according to claim 14 that contains the HBc amino acid residue sequence of position 1 through at least position 140, plus a single cysteine residue at the C-terminus.

16. (rejected) The recombinant HBc chimer protein molecule according to claim 15 wherein said chimer contains the HBc amino acid residue sequence of position 1 through position 149.

17. (rejected) The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

18. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 135 to about 515 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino

acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) one or more of residues 76 to 85 is absent;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii),

said chimer molecules self-assembling into particles on expression in a host cell, said particles being substantially free of binding to nucleic acids and more stable than are particles formed from otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an

amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

19. (rejected) The recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes.

20. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein said two heterologous epitopes are present in Domains I and II, II and IV or I and IV.

21. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope.

22. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a T cell epitope.

23. (rejected) The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope and the other is a T cell epitope.

24. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said Domain I includes a heterologous epitope peptide-bonded to one of HBc residues 1-4.

25. (rejected) The recombinant HBc chimer protein molecule according to claim 24 wherein said heterologous epitope of Domain II is a B cell epitope.

26. (rejected) The recombinant HBc chimer protein molecule according to claim 25 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

27. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope.

28. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope comprises up to about 245 amino acid residues.

29. (rejected) The recombinant HBc chimer protein molecule according to claim 28 wherein said heterologous epitope is a B cell epitope.

30. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 6 to about 50 amino acid residues.

31. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

32. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein said Domain IV comprises 1 to about 5 cysteine residues within about 30 residues from the C-terminus of the chimer molecule.

33. (rejected) The recombinant HBc chimer protein molecule according to claim 27 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

34. (cancelled)

35. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

36. (rejected) The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous linker residue for a conjugated epitope.

37. (rejected) The recombinant HBc chimer protein molecule according to claim 36 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

38. (rejected) The recombinant HBc chimer protein molecule according to claim 37 that contains a single cysteine residue at the C-terminus of the HBc chimer protein molecule.

39-41. (cancelled)

42. (rejected) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 175 to about 240 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) a cysteine residue [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said chimer molecules self-assembling into particles on expression in a host cell that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.2 to about 1.6 and are more stable than are particles formed from otherwise identical HBc

chimer molecules that lack said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

43. (rejected) The recombinant HBc chimer protein molecule according to claim 42 wherein said heterologous epitope of Domain II is a B cell epitope.

44. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 15 to about 50 amino acid residues.

45. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

46. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

47. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said B cell epitope is an amino acid sequence present in a pathogen selected from the group consisting of *Streptococcus pneumonia, Cryptosporidium parvum,* HIV, foot-and-mouth disease virus, influenza virus, *Yersinia pestis, Haemophilus influenzae, Moraxella catarrhalis, Porphyromonas gingivalis, Trypanosoma cruzi, Plasmodium falciparum, Plasmodium vivax, Plasmodium berghi, Plasmodium yoelli, Streptococcus sobrinus, Shigella flexneri,* RSV, *Plasmodium Entamoeba histolytica, Schistosoma japonicum, Schistosoma mansoni,* and ebola virus.

48. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

49. (rejected) The recombinant HBc chimer protein molecule according to claim 48 wherein said T cell epitope is from the organism against which a contemplated chimer is to be used as an immunogen.

50. (rejected) The recombinant HBc chimer protein molecule according to claim 43 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule.

51. (rejected) Immunogenic particles comprising recombinant hepatitis B core (HBc) chimeric protein molecules,

said chimeric protein molecules being up to about 515 amino acid residues in length, said chimeric protein molecules

(a) containing an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule,

(b) (i) displaying one or more heterologous immunogenic epitopes at the N-terminus, HBc immunogenic loop or C-terminus, or (ii) having a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop,

(c) containing a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus, and containing a cysteine residue at or near the C-terminus,

(d) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149,

said particle being substantially free of nucleic acid binding and exhibiting enhanced stability relative to particles comprised of otherwise identical proteins that are free of said cysteine residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days.

52. (rejected) The immunogenic particles according to claim 51 that exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7.

53. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the N-terminus.

54. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the C-terminus.

55. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope in the immunogenic loop.

56. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a B cell immunogenic epitope.

57. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays a T cell immunogenic epitope.

58. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein displays separate B cell and T cell immunogenic epitopes.

59. (rejected) The immunogenic particles according to claim 51 whose recombinant HBc chimeric protein has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop.

60. (rejected) The immunogenic particles according to claim 59 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

61. (rejected) The immunogenic particles according to claim 60 wherein said heterologous linker residue for a conjugated epitope is conjugated to a hapten.

62. (rejected) The immunogenic particles according to claim 61 wherein said hapten is an oligosaccharide.

63. (rejected) Immunogenic particles comprising a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules;

said recombinant chimeric HBc protein molecules having a length of up to about 515 amino acid residues that

(a) contain a HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues,

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contain a sequence of at least 5 amino acid residues from HBc position 135 through position 140 toward the HBc C-terminus,

said chimer molecules containing no more than 10 percent conservatively substituted amino acid residues in the HBc sequence, and

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from ~~an~~ otherwise identical HBc chimer molecules that lack said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecules is replaced by another residue, wherein said particle stability is assayed as a measurement of the percentage of full length chimer molecules determined by Coomassie Blue stain of reducing buffer 15%SDS-PAGE results obtained after dilution of purified particles to a concentration of 1 mg/mL in aqueous 50 mM $NaPO_4$, pH 6.8, with sodium azide added to a final concentration of 0.02% and incubation at 37° C for about 14 days, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

64. (rejected) The immunogenic particles according to claim 63 that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6.

65. (rejected) The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is about 175 to about 240 amino acid residues.

66. (rejected) The immunogenic particles according to claim 63 wherein said peptide-bonded heterologous epitope or

a heterologous linker residue for a conjugated epitope is a heterologous epitope.

67. (rejected) The immunogenic particles according to claim 66 wherein said heterologous epitope is a B cell epitope.

68. (rejected) The immunogenic particles according to claim 63 wherein the length of said recombinant chimeric HBc protein molecules is up to about 435 amino acid residues.

69. (rejected) The immunogenic particles according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBc.

70. (rejected) The immunogenic particles according to claim 67 wherein said B cell epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 5 residues of the HBc sequence of positions 76 through 85 are present.

71. (rejected) The immunogenic particles according to claim 70 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

72. (rejected) The immunogenic particles according to claim 68 further including a peptide-bonded heterologous T cell epitope.

73. (rejected) The immunogenic particles according to claim 72 wherein said T cell epitope is peptide-bonded to the C-terminal HBc amino acid residue.

74. (rejected) The immunogenic particles according to claim 73 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBc chimer protein molecule.

75. (rejected) The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 135 to about 515 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBc residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all of the residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBc and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBc at positions 76 to 85 is present free from heterologous residues;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

76. (rejected) The immunogenic particles according to claim 75 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.

77. (rejected) The immunogenic particles according to claim 76 wherein said hapten is a B cell immunogen.

78. (rejected) The immunogenic particles according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino acid residue

sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBc and constitute a heterologous epitope;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to about five cysteine residues [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus,

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6, and said chimeric HBc protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence corresponding to a sequence of SEQ ID NO:246-251 from position 1 through 149.

79-115. (cancelled)

EVIDENCE APPENDIX

None

RELATED PROCEEDING APPENDIX

None

Favorable consideration of this Appeal and allowance on the captioned application are respectfully requested.

Respectfully submitted,

By _____
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